Editorial

On the trail of the obesity paradox

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The obesity paradox refers to the phenomenon that overweight or obesity in patients with diseases, for which obesity and its metabolic sequelae constitute risk factors, may be protective and hence associated with decreased mortality. Gruberg *et al.* (1) observed that overall mortality was significantly higher in patients with coronary artery disease after percutaneous coronary intervention and normal body mass index (BMI) compared to overweight subjects. Since then, a number of studies, often encompassed by the term "reverse epidemiology", found that obesity or overweight, mostly defined by BMI, were associated with improved survival in chronic heart failure (CHF) (2), after acute myocardial infarction (3), and after cardiac surgery (4).

Noteworthy, significant heterogeneity was found across studies supporting the presence of the obesity paradox (5) and existence remains a point of debate, because it is mostly observed when BMI is used to define obesity. Inherent limitations of BMI as an index of adiposity, as well as methodological biases and the presence of confounding factors, may account for the observed discrepant findings of clinical studies. Importantly, BMI doses not take into account body composition phenotypes and metabolic variables. Nevertheless, it is clinically relevant to understand if and how obesity-related mechanism beneficially modulate pathophysiological processes leading to heart failure.

A high body fat ratio and certain fat distribution pattern, which are prevalent in subjects with high BMI, are correlated with a pro-inflammatory status. Systemic chronic low-grade inflammation is mechanistically linked to obesity related disease, e.g., atherosclerosis. Metabolic factors associated with obesity, e.g., hyperglycemia and hypercholesterinemia, elicit hematopoietic rewiring and epigenetic remodeling in bone marrow precursors (6-8). Moreover, the onset of obesity is characterized by accumulation of proinflammatory myeloid cells in many tissues (9). Clinically, obesity is associated with higher leukocyte blood counts and other markers of systemic inflammation which can already be observed in children (10).

Inflammation is a key component of both adverse myocardial remodeling after myocardial infarction and its systemic sequelae (11). Accordingly, several clinical studies revealed that the prognosis after myocardial infarction negatively correlates with measures of inflammation, e.g., blood monocyte levels predict on the outcome (12,13). The early healing phase after myocardial infarction is considered as critical determinant of future adverse remodeling and heart failure. Although the major source of blood myeloid cells under steady-state conditions is the bone marrow, monocytes immediately influx the heart from the spleen after myocardial infarction and the spleen becomes an organ of myelopoiesis (14). An extensive body of experimental evidence accumulated over the last years demonstrating a causative role of excess myelopoiesis, monocyte-derived macrophages and impaired healing (15,16). Therefore, one might hypothesize that obesity has adverse effects on myocardial healing and promotes adverse remodeling which would be seemingly contradictory to the obesity paradox.

Yang *et al.* (17) now report that feeding mice a high-fat diet (HFD) for 8 weeks provoked mild obesity not causing cardiac pathology. Mice subjected to such HFD developed less pronounced ventricular remodeling and systolic dysfunction 28 days post myocardial infarction. The number of total leukocytes within the heart was significantly lower in HFD mice at 7 days after myocardial infarction whereas the number of regulatory $CD4^+$ T cells was increased. Enhanced regulatory T cell recruitment promotes anti-

inflammatory macrophage differentiation and myocardial healing (18). Hence, the reported immunological findings could account for the overall protective effect of HFD after myocardial infarction and might even explain why obesity is protective in various chronic disease states. However, there are other contradictory finding in studies using HFD feeding protocols in experimental models of myocardial infarction. Thakker *et al.* reported enhanced left ventricular remodeling after myocardial ischemia-reperfusion in obese mice (19). Moreover, Mouton *et al.* described lower survival rates in obese male mice but less left ventricular dilation in surviving animals after myocardial infarction (20). The discrepant findings might partially rely on differences in the animal models used (ischemia-reperfusion *vs.* permanent coronary ligation, sex, strain, and metabolic characteristics). Therefore, before further investing in mouse studies, an in depth clinical characterization of patients after ST-elevation myocardial infarction (STEMI) allowing to correlate components of the metabolic syndrome and inflammation with infarct size and parameters describing myocardial healing and remodeling would be highly informative. This could be optimally achieved by a longitudinal characterization of a cohort of STEMI patients by cardiac magnetic resonance imaging combined by a thorough clinical phenotyping of the patients including parameters reflecting inflammation.

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